



Ophthalmics, Anti-Inflammatory/Immunomodulator Therapeutic Class Review (TCR)

June 5, 2017

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
cyclosporine (Restasis®, Restasis Multidose™) ^{1,2}	Allergan	Increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca
lifitegrast (Xiidra™) ³	Shire	Treatment of signs and symptoms of dry eye disease in adults

OVERVIEW

Keratoconjunctivitis sicca (KCS) is defined as dry eye disease (DED) related to either decreased tear volume (aqueous tear deficiency) or rapid evaporative loss (evaporative tear deficiency) due to poor tear quality. Both of these conditions may be present in dry eye syndrome (DES).⁴ The terms dry eye syndrome, dry eye disease, keratoconjunctivitis sicca, and keratitis sicca are often used interchangeably, with the term keratoconjunctivitis sicca being an older term. There is considerable overlap with other ophthalmic conditions, such as meibomian gland dysfunction.

DES/KCS affects approximately 10% to 30% of the United States (U.S.) population and occurs more commonly in patients over 40 years of age and in postmenopausal women.^{5,6} Patients with KCS/DES may have the following complaints: sensations of ocular dryness, grittiness, a foreign body, or irritation; hyperemia; mucoid discharge; excessive tearing; photophobia; and blurry vision. Some findings on examination consist of conjunctival hyperemia and fine, scattered loss of corneal or conjunctival epithelium.

Sjögren's syndrome, which can be a primary or secondary autoimmune disorder, often includes dry eye symptoms. DES associated with Sjögren's syndrome affects approximately 1% to 2% of the U.S. population. It also occurs more commonly in women. Neither agent in this review is indicated specifically for patients with Sjögren's syndrome.⁷

In tear-deficient DES/KCS, the inadequate tear production is typically idiopathic, but may also be secondary to a damaged or malfunctioning lacrimal gland or other autoimmune conditions.⁸ In evaporative DES/KCS, it is generally related to loss of the oily tear film, sometimes related to poor oil quality, such as in meibomian gland dysfunction or oil degradation (e.g., seborrheic blepharitis). Diagnosis is dependent on symptoms and clinical appearance. It may be further differentiated by the Schirmer test, which uses standardized strips of filter paper placed at the junction between the middle and lateral third of the lower lid. Five millimeters or less of wetting of the paper after 5 minutes on 2 successive occasions confirms the diagnosis of aqueous tear-deficient dry eye. The tear breakup test (TBUT) helps identify evaporative DES/KCS and uses fluorescein installation to coat the eye. The patient stares and the time to the first dry spot is determined. Accelerated tear film breakup (< 10 seconds) indicates evaporative DES/KCS.

In general, treatment is aimed to prevent corneal ulcers and scarring.⁹ Symptomatic treatment of KCS often includes the frequent application of viscous artificial tears and ointments. Multiple artificial tear products are available over-the-counter (OTC) and contain various formulations and strengths of cellulose to preserve viscosity, an agent to prevent evaporation (e.g., polyethylene glycol or an oil emulsion), and a preservative. Since there are various formulations, a patient may respond better to 1 agent than another, particularly if the patient is sensitive to certain preservatives or excipients. These products are available as drops, ointments, and gels and are dosed as needed based on symptoms.

Preservative-free options are also available.^{10,11} Prescription cyclosporine (Restasis, Restasis Multidose) and lifitegrast (Xiidra) provide treatment aimed at the cause of the dry eye symptoms rather than the symptomatic management.

According to the 2013 Preferred Practice Parameter on dry eye syndrome and the 2016 Cornea/External Disease Summary Benchmark from the American Academy of Ophthalmology (AAO), specific treatment recommendations depend on the severity and source of the dry eye.^{12,13} Typically, treatments are selected based on the severity level of the disease. Aqueous enhancement using artificial tear substitutes are recommended for *mild* DES. Preservative-free versions are preferred, when available, particularly if preservative versions are not tolerated or when used frequently. Other recommendations for mild dry eye include elimination of offending topical or systemic medications, eyelid therapy (e.g., warm compresses, eyelid hygiene), increased blinking, environmental changes (e.g., increasing humidity, avoiding air drafts), treatment of contributing ocular factors such as blepharitis or meibomianitis, and correction of eyelid abnormalities. Anti-inflammatory agents, including topical cyclosporine (Restasis, Restasis Multidose), or topical corticosteroids, or systemic omega-3 fatty acids supplements are recommended along with aqueous enhancement and other methods described above mild disease to be used for patients with *moderate* dry eyes. Other potential treatments for moderate dry eye include punctal plugs (lacrimal plugs) or spectacle side shields and moisture chambers. For *severe* dry eye, in addition to above mentioned treatments, systemic cholinergics, systemic anti-inflammatories, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, and tarsorrhaphy are recommended. Patient education is an important part of successful management of DES.

PHARMACOLOGY^{14,15,16}

While cyclosporine is known to be an immunomodulator when administered systemically, the exact mechanism in the management of KCS is unknown. Immunomodulating activity of cyclosporine is thought to reduce ocular inflammation. Topical cyclosporine (Restasis, Restasis Multidose) may take up to 4 to 6 weeks to demonstrate benefit.^{17,18}

The exact mechanism of lifitegrast (Xiidra), a lymphocyte function-associated antigen-1 (LFA-1) antagonist, in DED is unknown. Lifitegrast binds to LFA-1, blocking its interaction with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is thought to be overexpressed in DED, and its interaction with LFA-1 may lead to T-cell activation and migration. Based on available clinical trials, lifitegrast has demonstrated this benefit at 12 weeks; however, a quicker onset of efficacy cannot be ruled out.

PHARMACOKINETICS^{19,20,21}

Blood cyclosporine (Restasis, Restasis Multidose) concentrations in all samples collected, after topical administration of cyclosporine 0.05% twice daily for 12 months, were below the quantitation limit of 0.1 ng/mL.

Systemic exposure of lifitegrast (Xiidra) is minimal. Trough plasma concentrations were detectable in 19% of patients in a subset of patients with dry eyes on lifitegrast at steady state (range, 0.55 ng/mL to 3.74 ng/mL).

CONTRAINDICATIONS/WARNINGS^{22,23,24}

Cyclosporine (Restasis, Restasis Multidose) is contraindicated in patients with known hypersensitivity to cyclosporine or any excipient ingredients.

Lifitegrast (Xiidra) has no contraindications listed in the product labeling.

Cyclosporine ophthalmic emulsion and lifitegrast (Xiidra) should not be administered while wearing contact lenses. Patients should wait 15 minutes following drug administration to insert contact lenses. In addition, care should be taken not to touch the vial tip to the eye or other surfaces to avoid eye injury and contamination.

DRUG INTERACTIONS^{25,26,27}

No information is available in the prescribing information regarding drug interactions with either cyclosporine (Restasis, Restasis Multidose) or lifitegrast (Xiidra).

ADVERSE EFFECTS^{28,29,30}

The most common adverse effect with cyclosporine (Restasis, Restasis Multidose) is ocular burning (17%). Other reported adverse effects (1% to 5%) include conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbances (blurring).

The most common adverse reactions occurring in 5% to 25% of patients during clinical trials with lifitegrast (Xiidra) were instillation site irritation, dysgeusia, and decreased visual acuity.

SPECIAL POPULATIONS^{31,32,33}

Pediatrics

Safety and efficacy of cyclosporine (Restasis, Restasis Multidose) have not been established in children less than 16 years old. Safety and efficacy of lifitegrast (Xiidra) have not been established in pediatric patients less than 17 years old.

Pregnancy

Cyclosporine (Restasis in single-use containers) is Pregnancy Category C, while the cyclosporine (Restasis Multidose) and lifitegrast (Xiidra) have not been assigned a Pregnancy Category based on the Pregnancy and Lactation Labeling Rule (PLLR). Clinical administration of cyclosporine ophthalmic emulsion is not detected systemically; maternal use is not expected to result in fetal drug exposure. No human data are available on the use of lifitegrast in pregnant women to provide insight into drug-associated risks.

Geriatrics

No overall differences in safety or effectiveness were observed between geriatric and younger adults in clinical trials with either cyclosporine (Restasis, Restasis Multidose) or lifitegrast (Xiidra).

DOSAGES^{34,35,36,37}

Drug	Dosage	Comment	Availability
cyclosporine (Restasis, Restasis Multidose)	1 drop in each eye twice daily (12 hours apart)	Administer artificial tear products at least 15 minutes apart from cyclosporine ophthalmic emulsion Restasis Multidose: contains unidirectional valve and air filter; prime by squeezing 2 drops onto a tissue before initial use	0.05% ophthalmic emulsion in 0.4 mL single-use, preservative-free containers (trays of 30 or 60) Restasis Multidose: 5.5 mL of 0.05% ophthalmic emulsion in a 10 mL bottle (preservative-free)
lifitegrast (Xiidra)	1 drop in each eye twice daily (12 hours apart)	--	5% ophthalmic emulsion in 0.2 mL single-use, preservative-free containers (carton of 60 single-use containers stored in foil pouches of 5 containers/pouch)

The single-use containers should be discarded immediately after use.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

cyclosporine (Restasis) versus vehicle

Four randomized, vehicle-controlled, multicenter, clinical trials assessed the efficacy and safety of cyclosporine in approximately 1,200 patients with moderate to severe KCS whose tear production was suppressed due to ocular inflammation.³⁸ In these trials, cyclosporine demonstrated superiority over vehicle in Schirmer wetting of 10 mm at 6 months (approximately 15% with cyclosporine versus 5% with vehicle). Notably, increased tear production did not occur in patients using topical anti-inflammatory drugs or punctal plugs.

Cyclosporine 0.05% and 0.1% ophthalmic emulsions were compared to vehicle for efficacy and safety in 877 patients with moderate to severe DED over 6 months.³⁹ In these 2 identical, randomized, double-blind, multicenter trials, patients were administered treatment twice daily and evaluated based on corneal dye staining, Schirmer test, tear break-up time, ocular surface disease index, patient

subjective rating scale, symptoms of dry eyes, use of artificial tears, and investigator's evaluation of global response to treatment. Both cyclosporine arms provided significantly greater improvement on the corneal staining and Schirmer values than the vehicle group ($p \leq 0.05$). Subjective measures including blurred vision, need for artificial tears, and investigator's global assessment were greatly improved with cyclosporine 0.05% ($p \leq 0.05$). No dose-response relationship was observed. All therapies were well tolerated.

lifitegrast (Xiidra) versus vehicle

Four, 12-week, randomized, double-masked, vehicle-controlled, multicenter trials demonstrated the efficacy and safety of lifitegrast in DED ($n = 1,181$).^{40,41,42,43} Study 1, a dose-finding study, also included additional concentrations that are not commercially available; Study 1, which is a phase 2 trial, is not included in this review.⁴⁴ Study 2 (OPUS-1) and Study 3 (OPUS-2), both phase 3 trials, have also been published, but Study 4 has not been published. In all trials, patients with DED were randomized 1:1 to lifitegrast or vehicle twice daily. Use of artificial tears was not allowed. The mean age in all trials was 59 years (range, 19 to 97) and 76% were female. At each visit, patients rated their Eye Dryness Score (EDS) using a visual analog scale (VAS; 0 = no discomfort, 100 = maximum discomfort). Inferior Fluorescein Corneal Staining Score (ICSS) was also recorded at each visit (range, 0 [no staining] to 4 [coalescent]). At baseline, EDS scores ranged from 40 to 70 while mean ICSS scores ranged from 1.8 to 2.4. In Study 2, the difference in EDS at day 84 between vehicle and lifitegrast was -4.7 (95% CI, -8.9 to -0.4) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.23 (95% CI, -0.36 to -0.1). In Study 3, the difference in EDS at day 84 between vehicle and lifitegrast was -12.3 (95% CI, -16.4 to -8.3) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.03 (95% CI, -0.16 to 0.1). In Study 4, the difference in EDS at day 84 between vehicle and lifitegrast was -7.5 (95% CI, -11.6 to -3.5) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.17 (95% CI, -0.3 to -0.03). Thus, a statistically significant difference was found between vehicle and lifitegrast in EDS in all 3 trials and in ICSS in 2 of 3 trials.

SUMMARY

Keratoconjunctivitis sicca, or dry eye syndrome, is defined as DED related to either decreased tear volume (aqueous tear deficiency) or rapid evaporative loss (evaporative tear deficiency) due to poor tear quality. Both of these conditions may be present as well. The terms keratoconjunctivitis sicca (an older term) and dry eye syndrome are used somewhat interchangeably. Thus, the role in therapy, or indication, of lifitegrast (Xiidra) is highly similar to that of topical cyclosporine (Restasis, **Restasis Multidose**). However, lifitegrast is approved for both the signs and symptoms of DED, while cyclosporine is approved to treat inflammation associated with DED and enhances tear production.

Significant adverse effects are similar between the 2 agents in this class and primarily include ocular burning or irritation upon instillation. Neither agent has been compared in published clinical trials, but both have demonstrated efficacy against vehicle. Topical cyclosporine may take up to 4 to 6 weeks to demonstrate benefit. Published clinical trials of lifitegrast evaluated outcomes primarily at 12 weeks; it is unknown if a clinically significant improvement may occur sooner.

Both agents may offer relief from DED and are used twice daily. Clinical practice guidelines have not yet addressed the role of lifitegrast; however, guideline recommend topical cyclosporine for moderate and severe dry eye syndrome, in addition to other treatment measures.

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